PROVES DIAGNÒSTIQUES DE M.A.F.L.D.

- Criteris diagnòstics MAFLD
- Prevalença i mortalitat per MAFLD i DBT
- Fisiopatologia de MAFLD
- Manifestacions extrahepàtiques de MAFLD
- Factors predictors de NAFLD
- Comorbiditats associades a NAFLD (MCV i IRC)
- Paràmetres valorables MAFLD
- Tests no invasius per valorar la Fibròsi /Esteatòsi hepàtica
- Proves d´imatge no invasives
- Opcions terapèutques MAFLD

From NAFLD to __MAFLD__

NAFLD

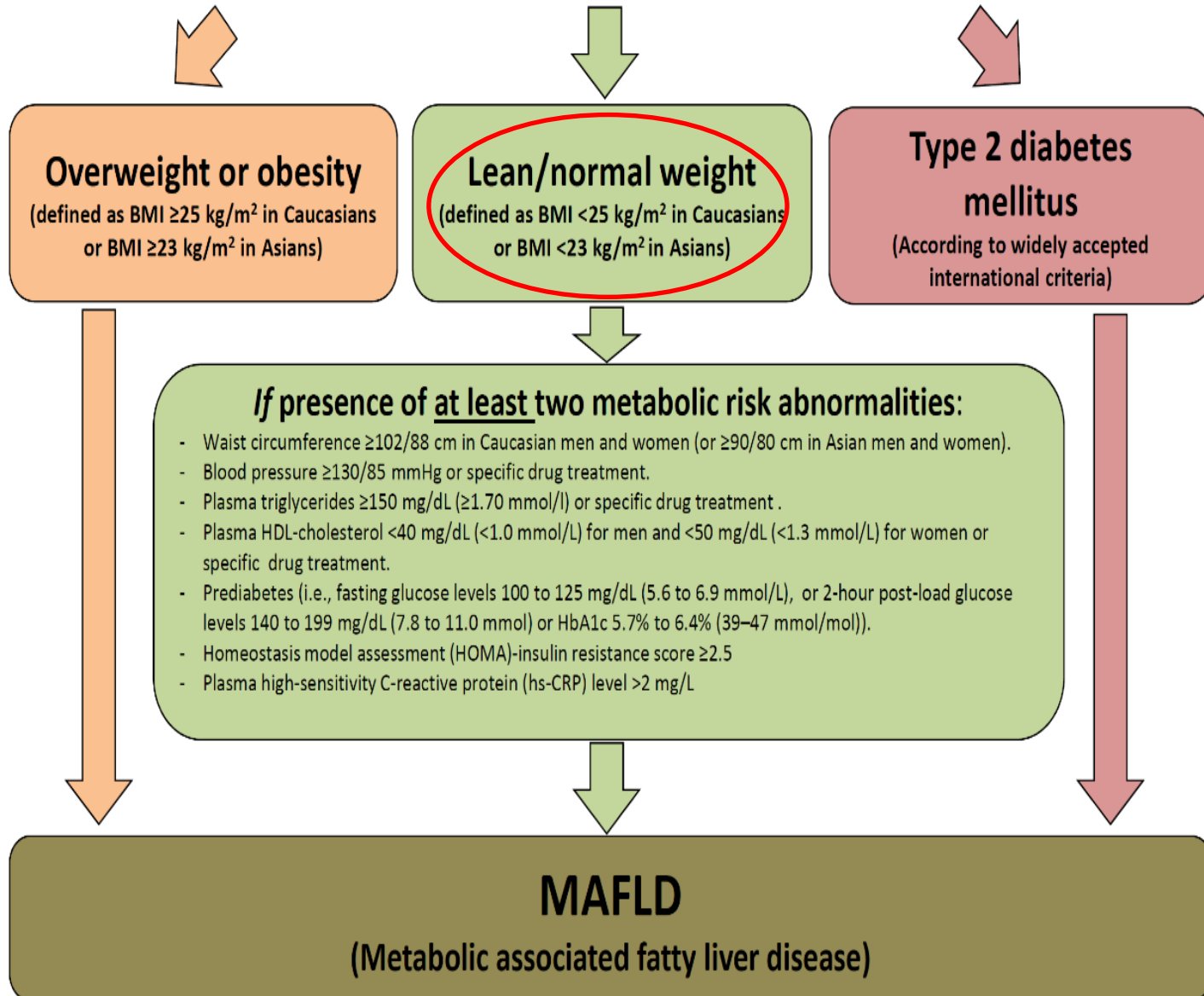- Diagnosis of exclusion
  - Not caused by HCV, HBV, alcoholic liver disease

Hepatic Steatosis

MAFLD

- Positive diagnosis
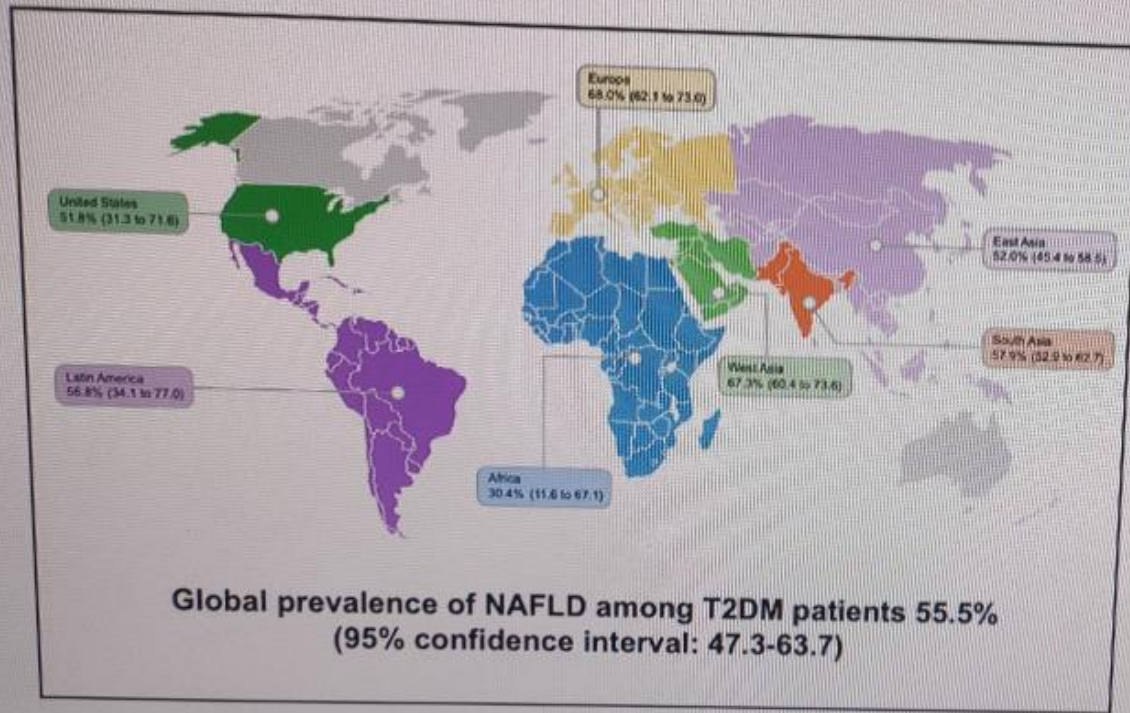 - Caused by **overweight/obesity, diabetes mellitus,** or ≥**2 metabolic risk abnormalities**

Hepatic steatosis in adults
(detected either by imaging techniques, blood biomarkers/scores or by liver histology)

Overweight or obesity
(defined as BMI ≥ 25 kg/m^2 in Caucasians or BMI ≥ 23 kg/m^2 in Asians)

Lean/normal weight
(defined as BMI <25 kg/m^2 in Caucasians or BMI <23 kg/m^2 in Asians)

Type 2 diabetes mellitus
(According to widely accepted international criteria)

If presence of <u>at least</u> two metabolic risk abnormalities:

- Waist circumference $\geq 102/88$ cm in Caucasian men and women (or $\geq 90/80$ cm in Asian men and women).
- Blood pressure $\geq 130/85$ mmHg or specific drug treatment.
- Plasma triglycerides ≥ 150 mg/dL (≥ 1.70 mmol/l) or specific drug treatment .
- Plasma HDL-cholesterol <40 mg/dL (<1.0 mmol/L) for men and <50 mg/dL (<1.3 mmol/L) for women or specific drug treatment.
- Prediabetes (i.e., fasting glucose levels 100 to 125 mg/dL (5.6 to 6.9 mmol/L), or 2-hour post-load glucose levels 140 to 199 mg/dL (7.8 to 11.0 mmol) or HbA1c 5.7% to 6.4% (39–47 mmol/mol)).
- Homeostasis model assessment (HOMA)-insulin resistance score ≥ 2.5
- Plasma high-sensitivity C-reactive protein (hs-CRP) level >2 mg/L

MAFLD
(Metabolic associated fatty liver disease)

PREVALENÇA DE M.A.F.L.D. (70%) EN DIABETES

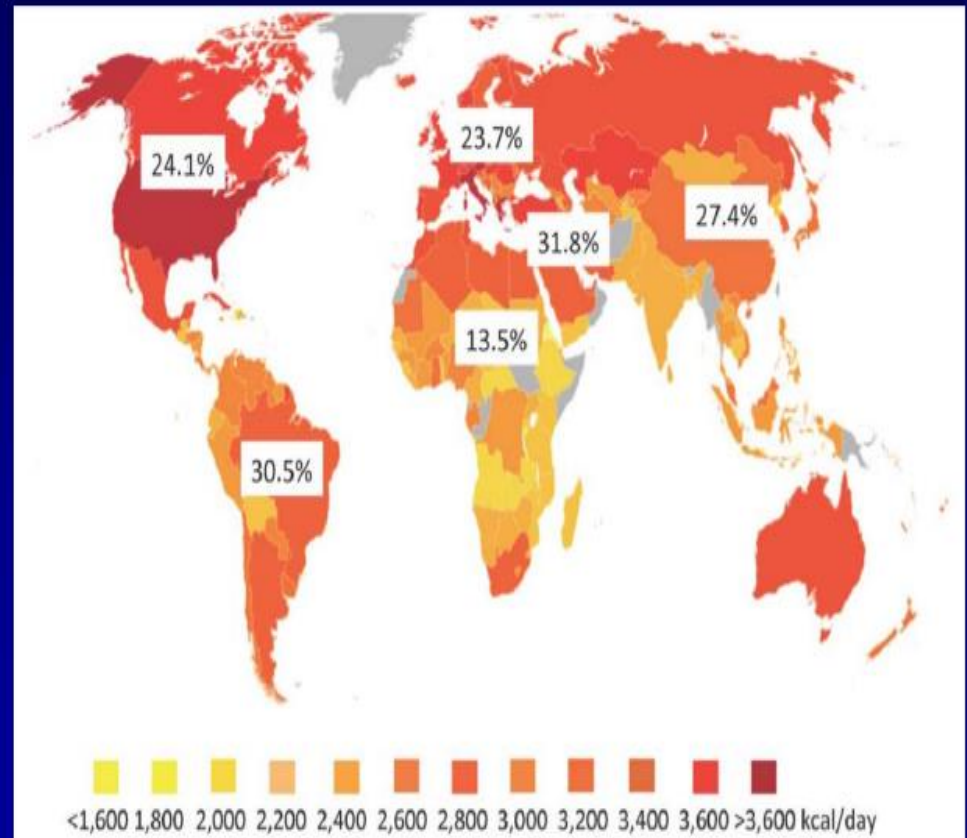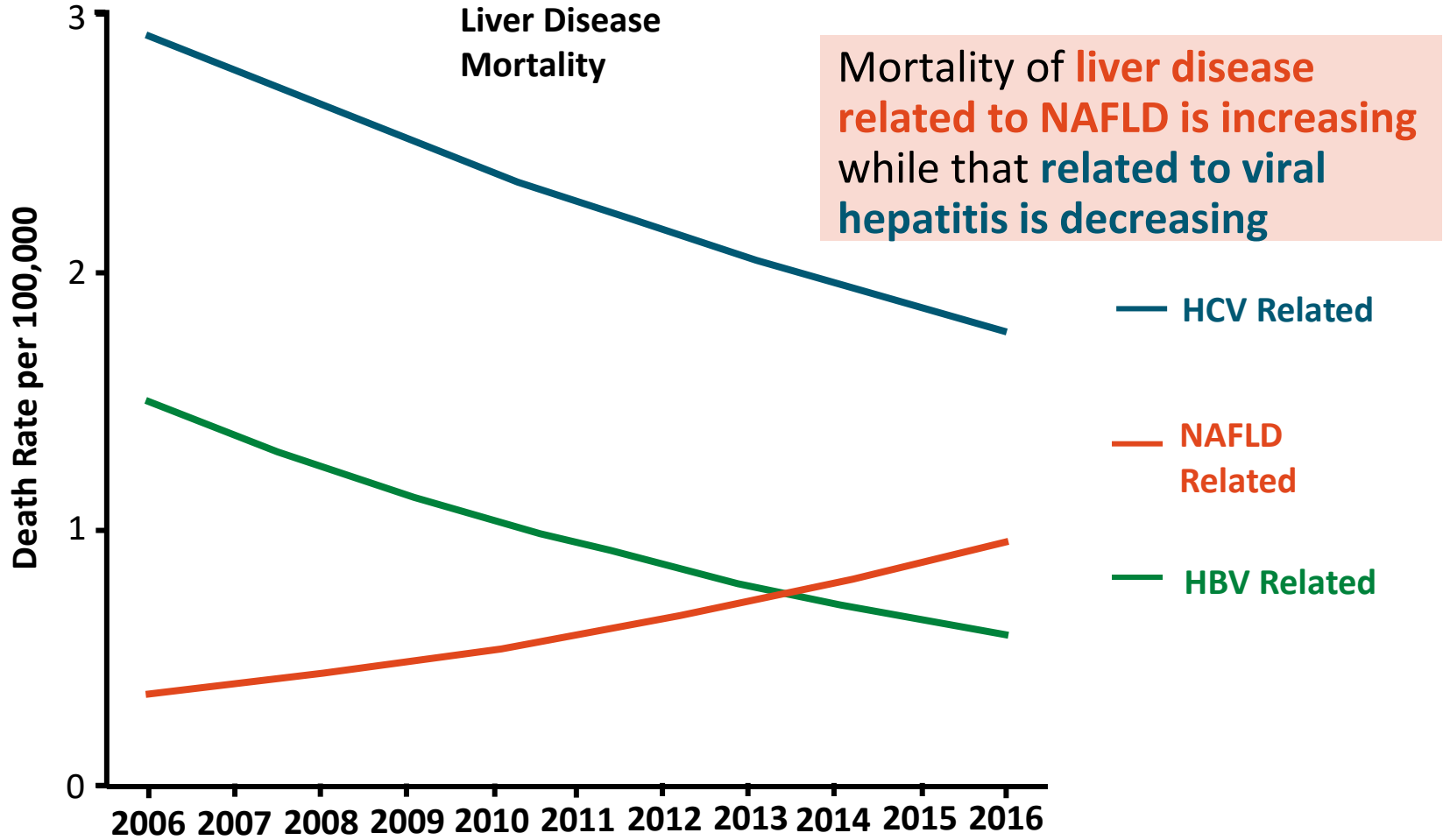Global prevalence of MASLD among T2DM patients

Meta-analysis 80 studies, 20 countries

- 49,419 individuals with T2DM
- Prevalence MASLD: 2x general population
- MASH: 37.3% (n = 892)
- Advanced fibrosis: 17% (n= 439)

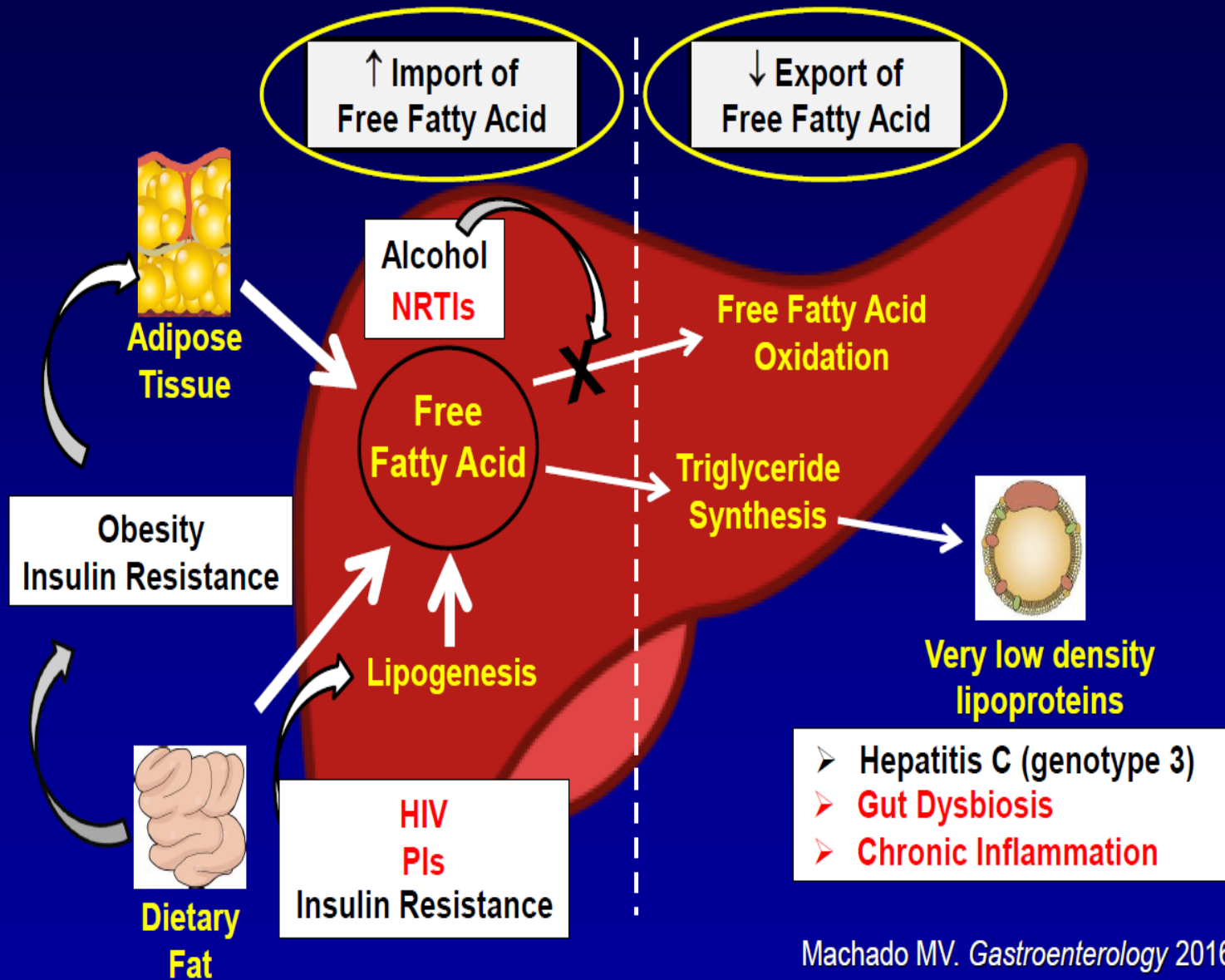Global prevalence of NAFLD among T2DM patients 55.5% (95% confidence interval: 47.3-63.7)

Younossi et al, JHEP 2019

Fatty Liver Highly Prevalent Worldwide

- **NAFLD prevalence: 25%**

- **NAFLD associated with:**
  - ↑ caloric excess
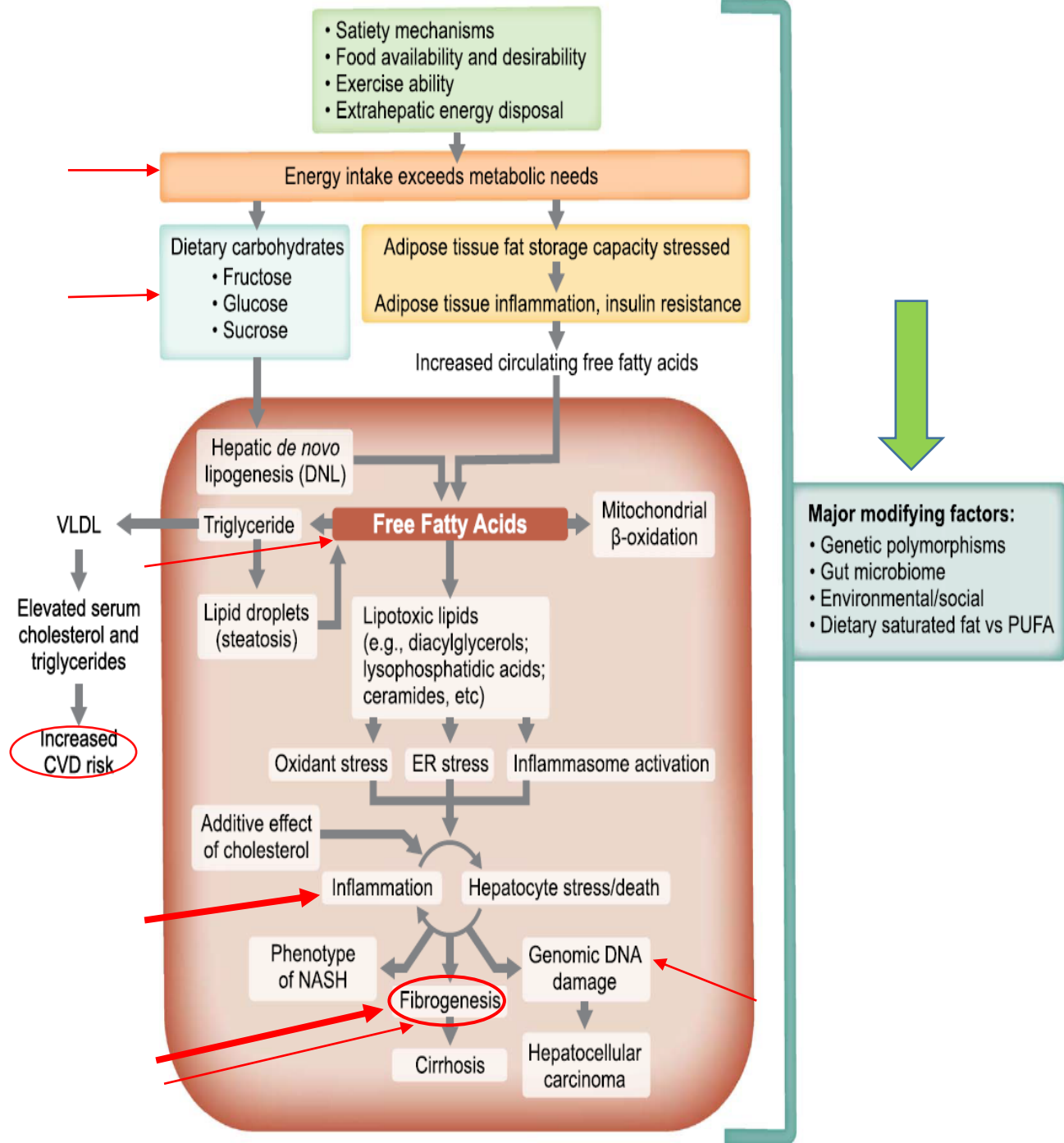 - metabolic syndrome
  - genetic predisposition

24.1%

23.7%

27.4%

31.8%

13.5%

30.5%

<1,600 1,800 2,000 2,200 2,400 2,600 2,800 3,000 3,200 3,400 3,600 >3,600 kcal/day

Younossi Z. *Hepatology* 2016; 64:73-84.

Viral Hepatitis and Presumed NAFLD Among Medicare Beneficiaries With HIV: <u>Mortality</u>

Liver Disease Mortality

Mortality of **liver disease related to NAFLD is increasing** while that **related to viral hepatitis is decreasing**

— **HCV Related**

— **NAFLD Related**

— **HBV Related**

Paik. Open Forum Infect Dis. 2020;7:ofz509.

Pathogenesis of Fatty Liver in PWH

↑ Import of Free Fatty Acid

↓ Export of Free Fatty Acid

Adipose Tissue

Alcohol
NRTIs

Free Fatty Acid

Free Fatty Acid Oxidation

Triglyceride Synthesis

Obesity
Insulin Resistance

Lipogenesis

Very low density lipoproteins

Dietary Fat

HIV
PIs
Insulin Resistance

- ➢ Hepatitis C (genotype 3)
- ➢ Gut Dysbiosis
- ➢ Chronic Inflammation

Machado MV. *Gastroenterology* 2016;150:1769-77.
Verna E. *Lancet Gastroenterol Hepatol* 2017;2:211-23.

- Satiety mechanisms
- Food availability and desirability
- Exercise ability
- Extrahepatic energy disposal

Energy intake exceeds metabolic needs

Dietary carbohydrates
- Fructose
- Glucose
- Sucrose

Adipose tissue fat storage capacity stressed

Adipose tissue inflammation, insulin resistance

Increased circulating free fatty acids

Hepatic *de novo* lipogenesis (DNL)

VLDL

Triglyceride

Free Fatty Acids

Mitochondrial β-oxidation

Elevated serum cholesterol and triglycerides

Lipid droplets (steatosis)

Lipotoxic lipids (e.g., diacylglycerols; lysophosphatidic acids; ceramides, etc)

Increased CVD risk

Oxidant stress

ER stress

Inflammasome activation

Additive effect of cholesterol

Inflammation

Hepatocyte stress/death

Phenotype of NASH

Fibrogenesis

Genomic DNA damage

Cirrhosis

Hepatocellular carcinoma

Major modifying factors:
- Genetic polymorphisms
- Gut microbiome
- Environmental/social
- Dietary saturated fat vs PUFA

EVOLUCIÓ i MORTALITAT DE LA M.A.F.L.D.

Injury

Virus Hepatotrops
Alcohol
MAFLD

Hepatocytes

Injured hepatocytes

Space of Disse

DAMPs
Apoptotic bodies

Activated
HSC

ECM
deposit

Quiescent
HSC

PDGF
TGF-β

Proliferation

Survival

Mutual
stimulation

Infiltration

Proliferation
Cytokine secretion

Recruitment
Cytokine secretion T cells

CCL2
Cytokines

Monocyte

Kupffer
cells

Recruitment

Sinusoidal
endothelial cells

The NAFLD Continuum:
NAFLD, NASH, Cirrhosis More Prevalent in PWH

NAFLD

Normal Liver	**Steatosis "NAFL"**	**Steatohepatitis "NASH"**	**Cirrhosis**
	Fatty liver with trivial or no inflammation and no hepatocyte ballooning	Fatty liver with significant inflammation and hepatocyte ballooning	Increasing fibrosis leading to cirrhosis, hepatocellular carcinoma (sometimes loss of fat)
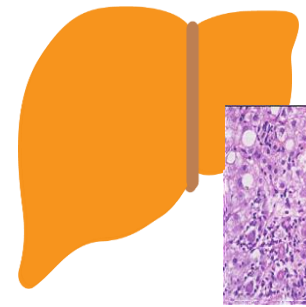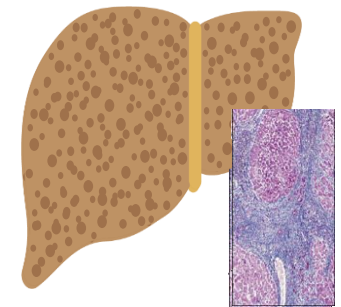
Worldwide prevalence:	**25%[1,2]**	**3% to 5%[1]**	**1% to 2% at risk***
Prevalence in HIV:	**3% to 65%[2]**	**10%[3]**	**2.3-6% at risk[2]**

*Based on analysis of NHANES data estimating 1.74% prevalence of NASH with advanced fibrosis.[4]

1. Younossi. J Hepatol. 2019;70:531. 2. Cervo. Curr HIV/AICS Rep. 2020;17:601.
3. Benmassaoud. PLoS ONE. 2018;13:e0191985. 4. Kabbany. Am J Hepatol. 2017;112:581.
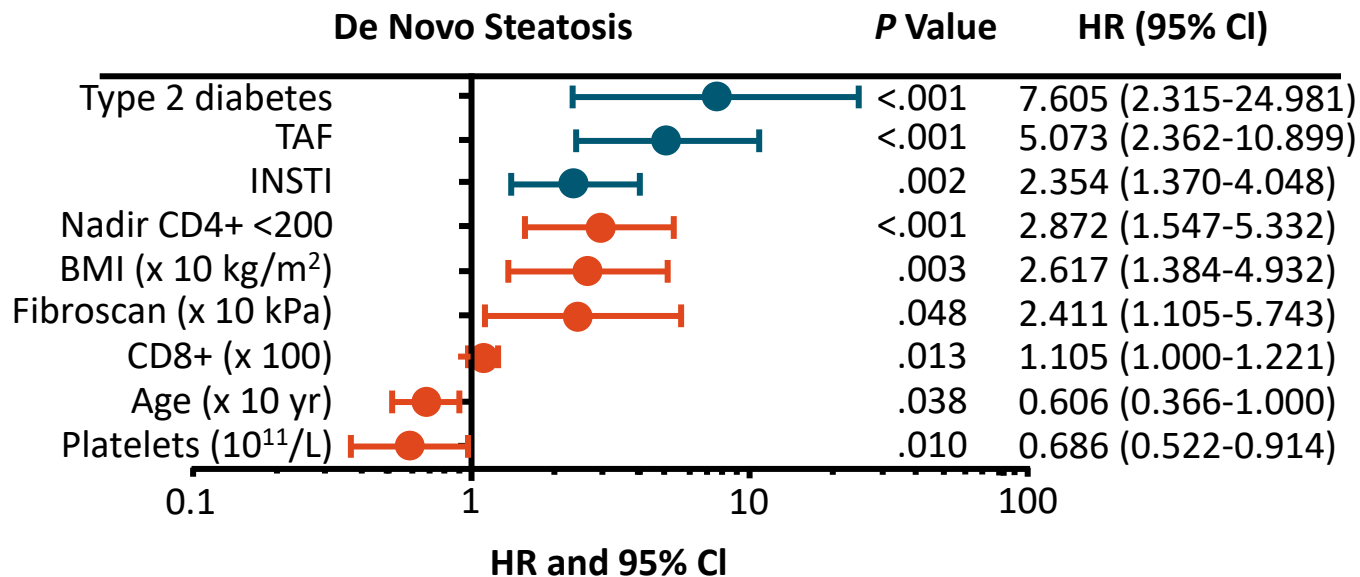
Association Between NAFLD and Extrahepatic Manifestations

Obesitat
Dislipidèmia
Hiperuricèmia
HTA
Alcohol
Fibrosis
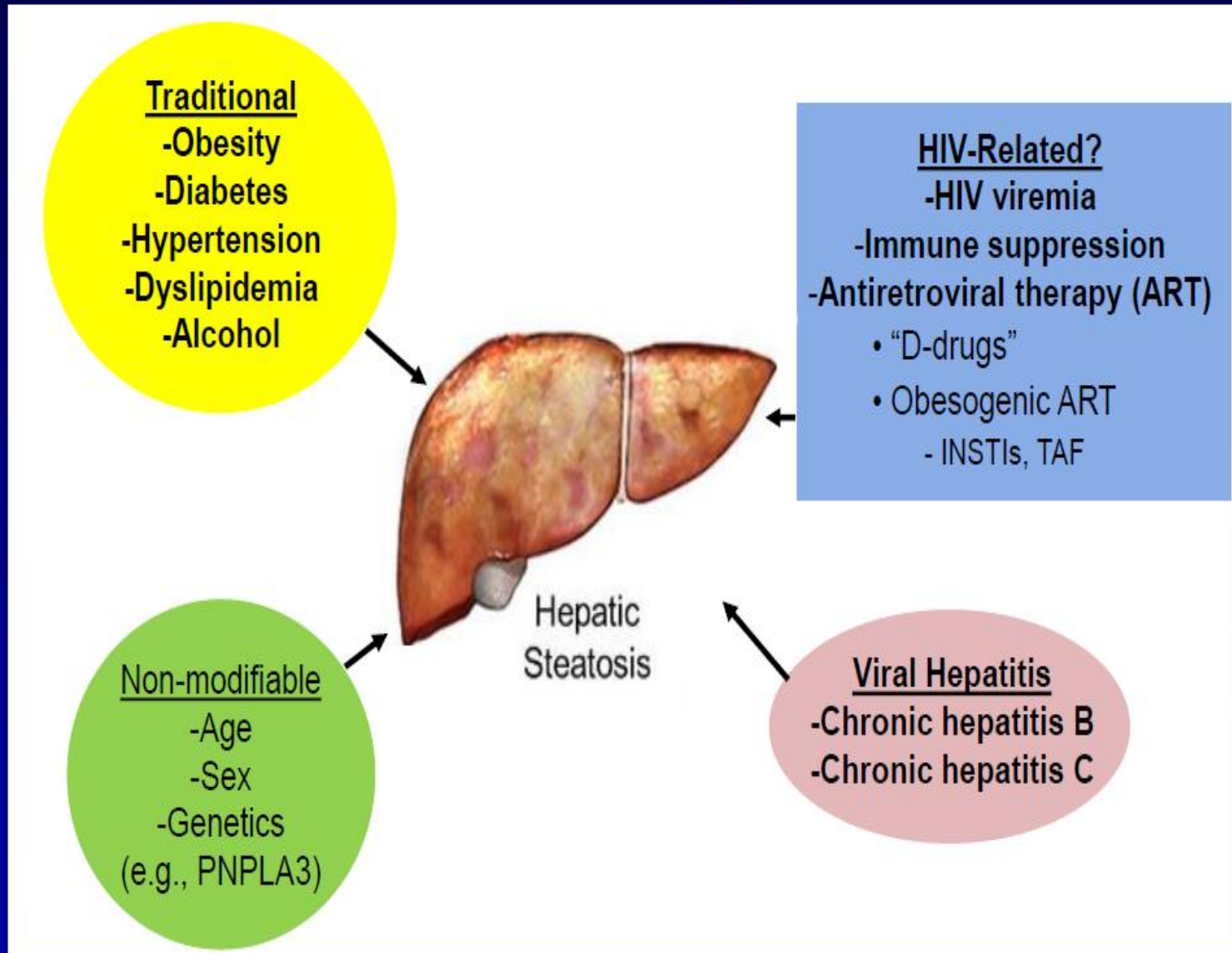Hipotiroidisme
Dèficit de GH
Hipogonadisme
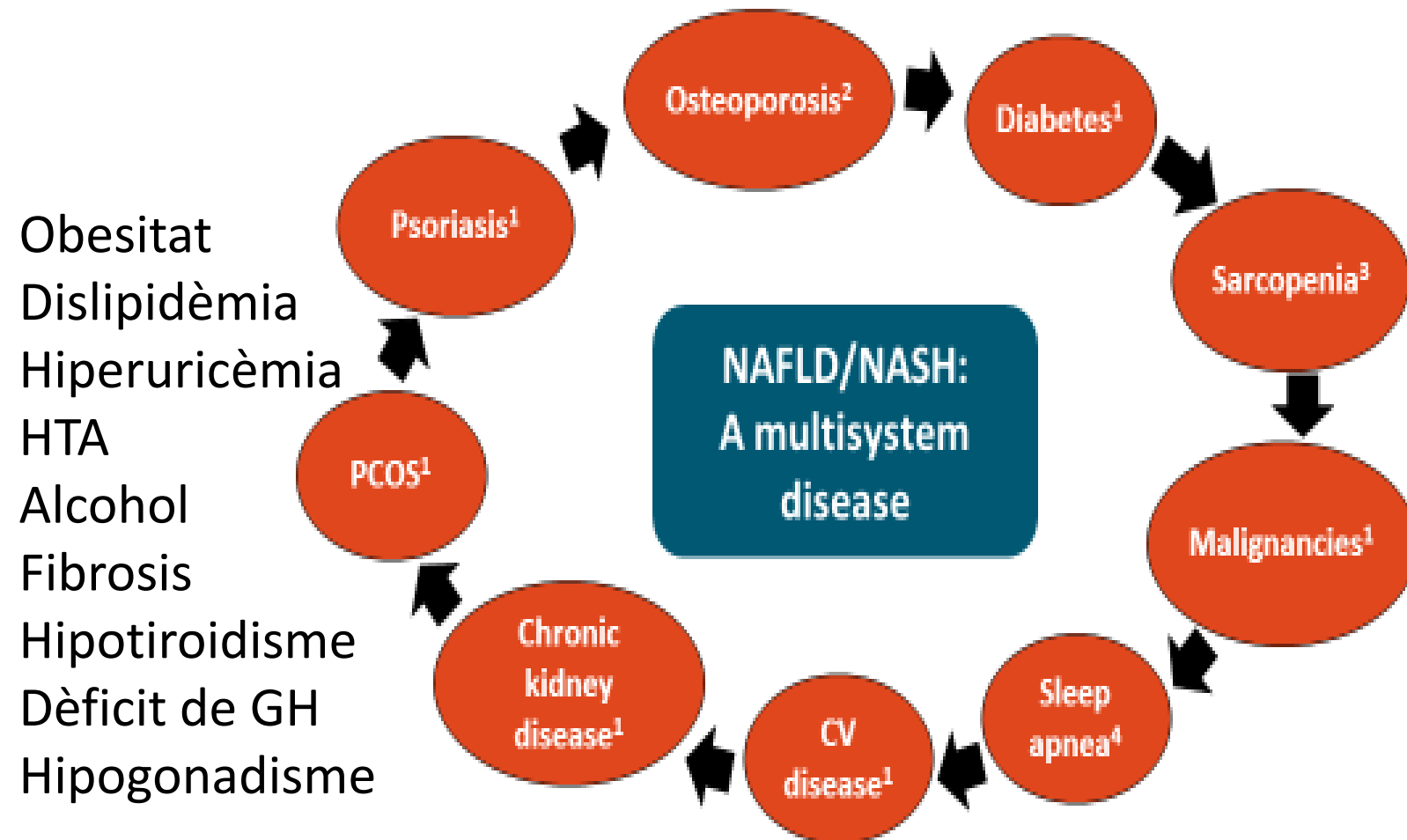
1. Andrew. Gut Liver. 2020;14:168. 2. Filip. Clin Interv Aging. 2018;13:1879.
3. Andrew. Clin Liver Dis. 2020;16:73. 4. Umbro. World J Gastroenterol. 2020;26:2669.

Risk Factor Determination for De Novo Steatosis

- Patients with HIV monoinfection (N = 301) evaluated by serial Fibroscan with CAP; mean follow-up 41.8 ± 14.8 mo

De Novo Steatosis	P Value	HR (95% CI)
Type 2 diabetes	<.001	7.605 (2.315-24.981)
TAF	<.001	5.073 (2.362-10.899)
INSTI	.002	2.354 (1.370-4.048)
Nadir CD4+ <200	<.001	2.872 (1.547-5.332)
BMI (x 10 kg/m^2)	.003	2.617 (1.384-4.932)
Fibroscan (x 10 kPa)	.048	2.411 (1.105-5.743)
CD8+ (x 100)	.013	1.105 (1.000-1.221)
Age (x 10 yr)	.038	0.606 (0.366-1.000)
Platelets (10^{11}/L)	.010	0.686 (0.522-0.914)

HR and 95% CI

Bischoff. eClinicalMed. 2021;40:101116.

Risk Factors for Fatty Liver in PWH

Traditional
-Obesity
-Diabetes
-Hypertension
-Dyslipidemia
-Alcohol

HIV-Related?
-HIV viremia
-Immune suppression
-Antiretroviral therapy (ART)
- • "D-drugs"
- • Obesogenic ART
  - INSTIs, TAF

Non-modifiable
-Age
-Sex
-Genetics
(e.g., PNPLA3)

Viral Hepatitis
-Chronic hepatitis B
-Chronic hepatitis C

Hepatic Steatosis

Perazzo H. *J Int AIDS Soc*. 2018;21:e25201
Grunfeld C. *Am J Med*. 1989;86:27-31; Lake JE. *Clin Gastroenterol Hepatol*. 2022;20:256-268

LIVEHIV Cohort: High BMI Main Predictor of Hepatic Steatosis Progression in PWH

- Prospective cohort study in Canada, screening PWH (n = 313) for **hepatic steatosis** and **liver fibrosis** using CAP and TE

    - Median follow-up 15.4 mo

Independent predictor of progression of steatosis

- **BMI (per kg/m^2)** aHR: 1.09 (95% CI: 1.03-1.17)

Independent predictors of progression of fibrosis

- **Duration of HIV infection (per 10 yr)** aHR: 1.43 (95% CI: 1.02-2.12)

- **Presence of hepatic steatosis** aHR: 4.18 (95% CI: 1.21-14.5)

Pembroke. J Hepatol. 2017;67:801.

RELACIÓ ENTRE NAFLD i MCV + IRC
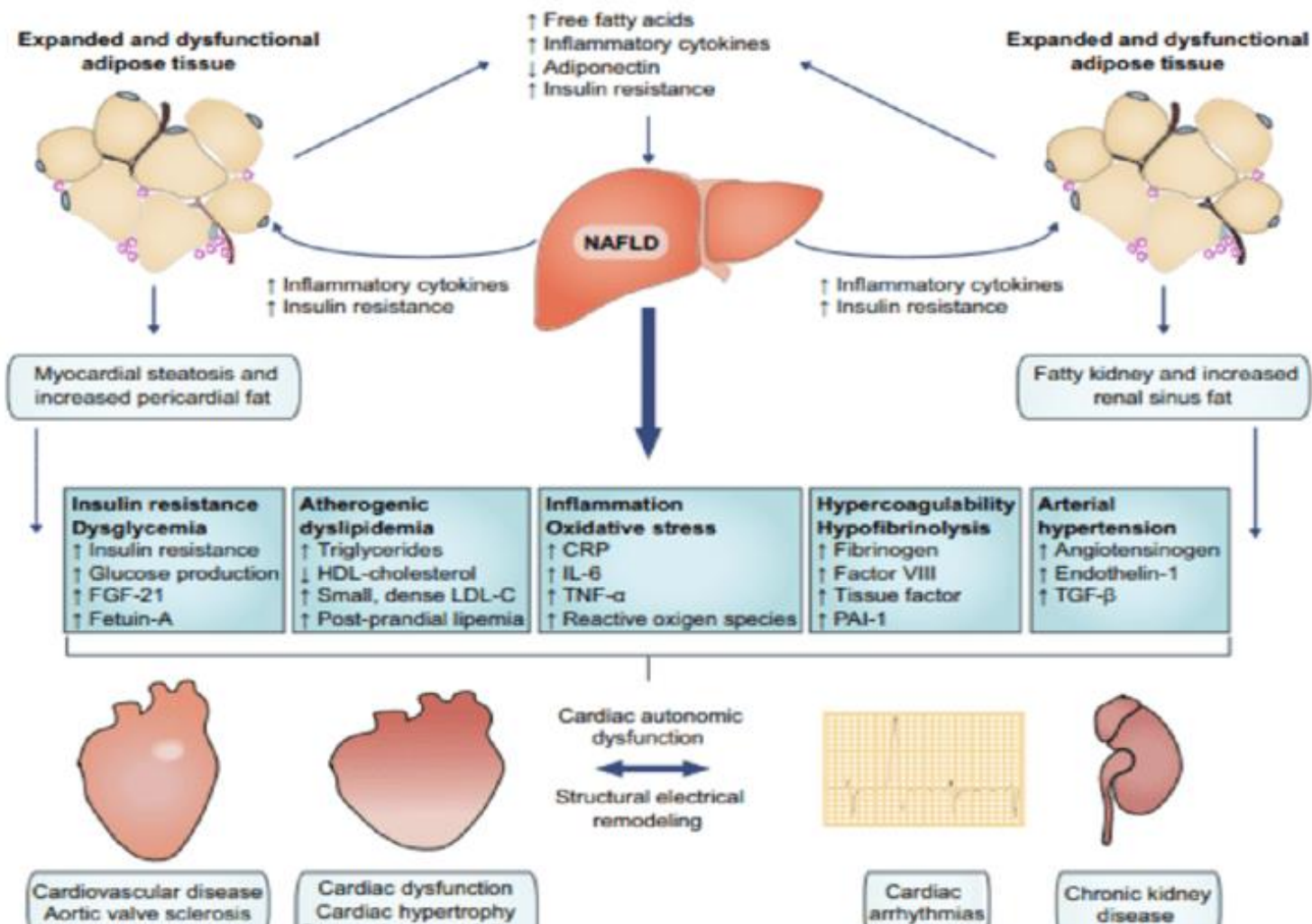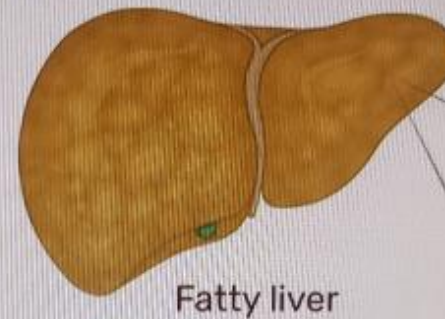
RELACIÓ ENTRE MASLD i DBT-II
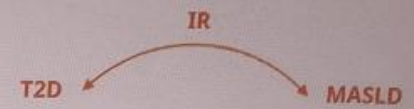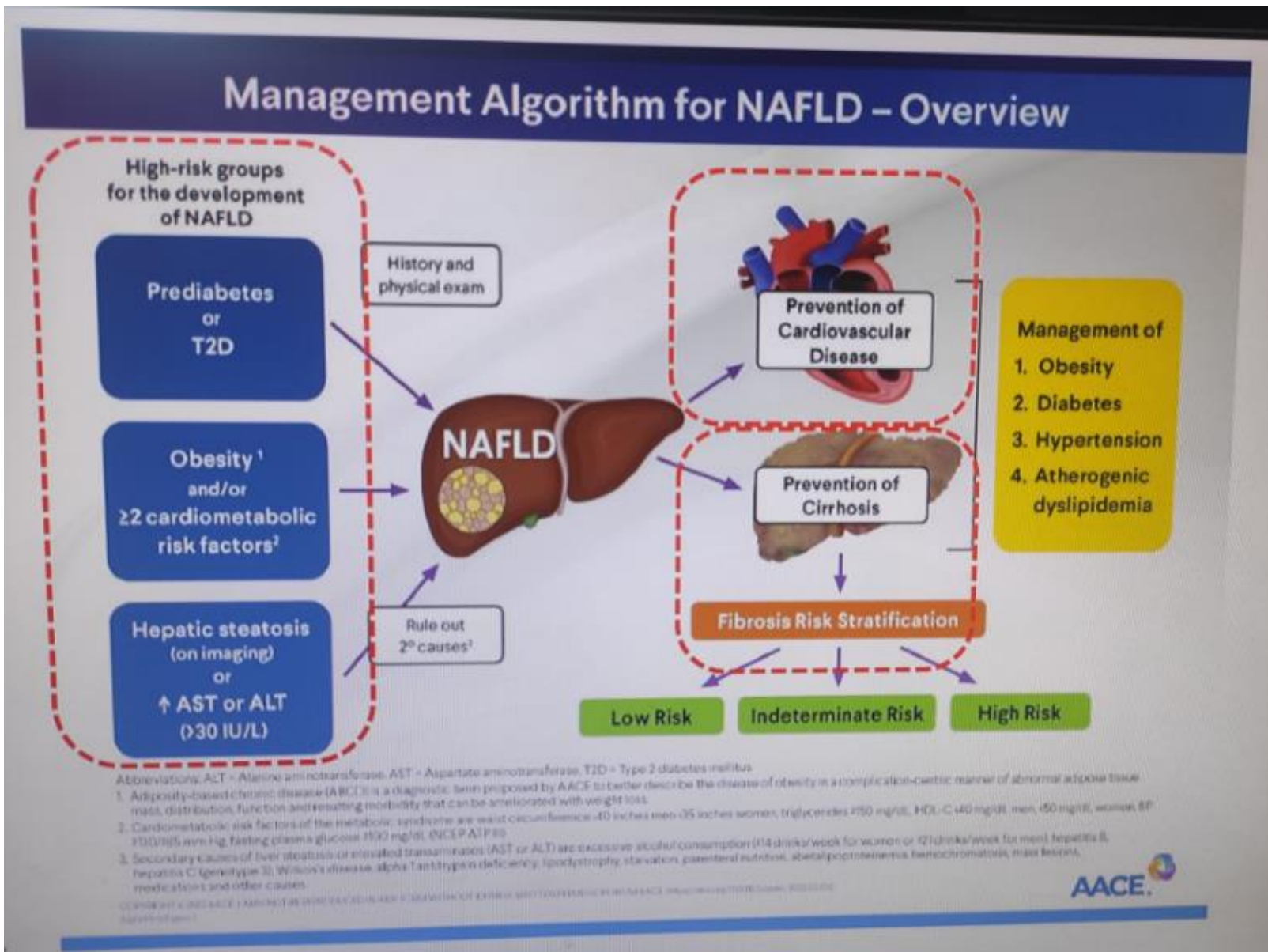
RELACIÓ MASLD - MCV

MASLD and the Heart

More asCVD in MASLD:

- support from non-invasive studies – cIMT, CAC
- prospective cohorts – more events
- asCVD main cause of death, not liver-related events
- *no* increased risk of asCVD death

Fatty liver

Atherosclerosis

For review: Stols-Goncalves, Holleboom, Trends in Endo & Metab 2019
Driessen, Drenth, Anker, Tushuizen, Holleboom, Hepatology 2023

OPCIONS TERAPÈUTIQUES NAFLD + MCV

RELACIÓ ENTRE ALCOHOL I MAFLD
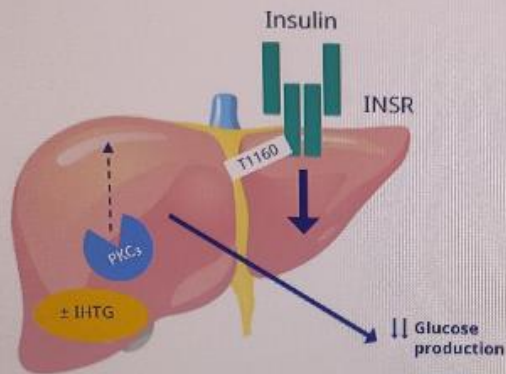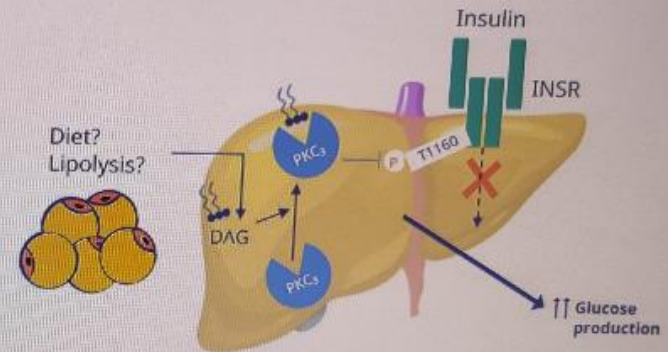
Enfermedad por esteatosis hepática (SLD, del inglés Steatotic Liver Disease)

Enfermedad por esteatosis hepática asociada a disfunción metabólica (MASLD)

MetALD (MASLD con incremento de ingesta de alcohol*)

Predominio MASLD | Predominio ALD
140/210   210   280   350/420
Ingesta de alcohol semanal (g)

Predominio MASLD | Predominio ALD
20/30   30   40   50/60
Ingesta promedio de alcohol diario (g)

Enfermedad hepática asociada (relacionada) a Alcohol (ALD)

Enfermedad por esteatosis hepática por etiologías especificas
- Injuria hepática inducida por drogas
- Enfermedades monogénicas **
- Misceláneo***

Enfermedad por esteatosis hepática criptogénica

*Ingesta semanal 140-350g en mujeres, 210-420g en hombres (promedio diario 20-50g en mujeres, 30 – 60g en hombres)
**e.j. Deficiencia de lipasa acida lisosomal (LALD), enfermedad de Wilson, hipobetalipoproteinemia, errores innatos del metabolismo
***e.j. Virus Hepatitis C (VHC), malnutrición, enfermedad celiaca

Adaptado de Rinella, M. E., et al., A multi-society Delphi consensus statement on new fatty liver disease nomenclature. Hepatology. 2023 Jun 24, doi: 10.1097/HEP. 000000000000520. Epub ahead of print. PMID: 37363821

Fatty Liver ↑ Risk of Hepatocellular Carcinoma

- Retrospective cohort – all US Veterans

  – NAFLD: alanine aminotransferase (ALT) ≥40 IU/mL x 2 for ≥6 months

  – Excluded viral hepatitis, alcohol

- 296,707 matched 1:1 to controls

- Median follow-up: 9 years

Risk of HCC Among US Veterans in care, 2004-2015

Characteristic	Adjusted Hazard Ratio (95% Confidence Interval)
NAFLD	7.6 (5.8-10.1)
Age ≥65 years	1.8 (1.5-2.2)
Hispanic ethnicity	1.6 (1.1-2.2)
Obesity	1.2 (1.0-1.4)
Diabetes	3.0 (2.5-3.6)
Hypertension	1.1 (0.8-1.4)

HCC Incidence: 0.21 per 1,000 person-years with NAFLD
0.02 per 1,000 person years without NAFLD

PARAMÈTRES PREVIS VALORABLES PER MAFLD

- **- Valors antropomètrics :**

  – Pes, alçada (IMC > 25) i perímetre de cintura (> 102 / 88 cm.)

  – **Valors Analítics :**

  – *Perfil lipídic*: Colesterol T. > 250 mg./dl.

  Colesterol – HDL < 40 mg./dl.

  Triglicèrids > 150 mg./dl.

  - *Perfil glucèmic*: G > 110 mg./dl. Hgb A1C > 6´5

  Test de HOMA-IR (G, Insulinèmia) > 2´5

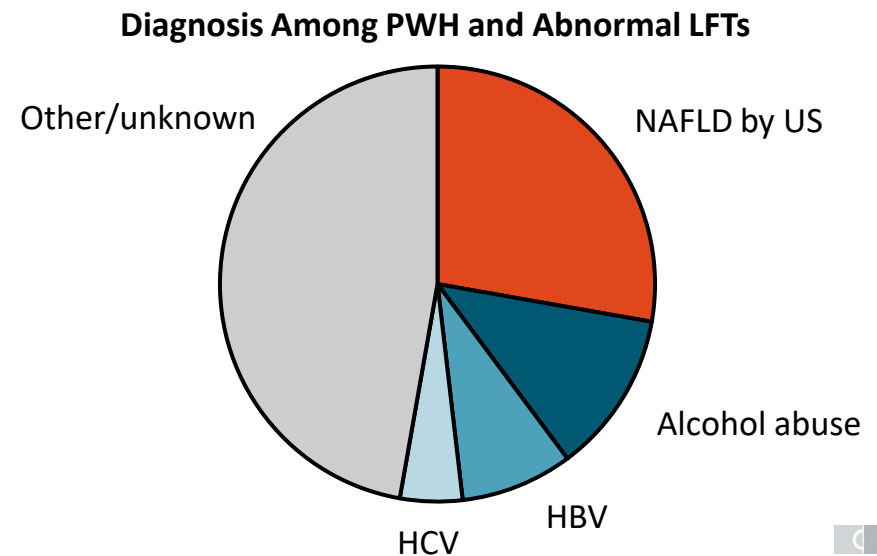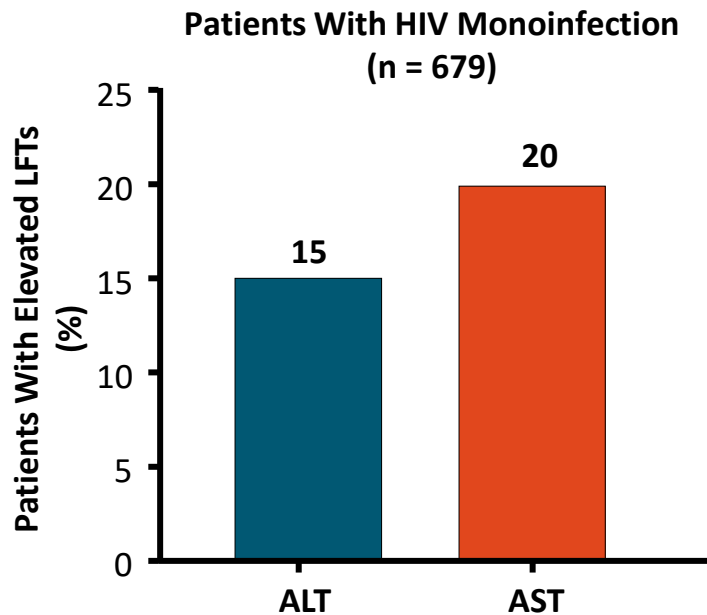 - *Perfil hematològic*: Plaquetes

  - *Perfil hepàtic*: ↑ AST / ALT

  Qüocient AST / ALT < 1

Elevated Liver Transaminases in PWH: Caused by NAFLD

- Retrospective, single-center study of PWH (N = 1208)[1]

- Cross-sectional, single-center study of PWH (N = 299)[2]
  - In 6-mo study period, 27% had abnormal LFTs

Patients With HIV Monoinfection (n = 679)

Diagnosis Among PWH and Abnormal LFTs

1. Sterling. Dig Dis Sci. 2008;53:1375. 2. Crum-Cianflone. Clin Gastroenterol Hepatol. 2010;8:183.

Available Noninvasive Tests for Hepatic Steatosis and Liver Fibrosis

| Serum Biomarkers: Clinical or Laboratory Scores		Imaging
Simple	**Proprietary**	**Elastography**
▪ Fibrosis-4[1,3]	▪ ELF test[1] (not available in US)	▪ Transient elastography (eg, *FibroScan, CAP*)[1,2]
▪ NAFLD fibrosis score[1,2]	▪ NIS4	▪ 2D shear wave elastography[5]
▪ APRI[1]	▪ ADAPT/Pro-C3[4] (not available in US)	▪ Magnetic resonance elastography[1]
▪ BARD score[3]	▪ *FibroSure*[1]	▪ Corrected T1 (*Liver MultiScan*)[6,7]
	▪ Hepascore	▪ MRI-PDFF[8]
		▪ FAST score[9]

Many of these lab values are part of routine assessments in PWH

1. EASL. J Hepatol. 2015;63:237. 2. Alkhouri. Gastroenterol Hepatol (N Y). 2012:8:661. 3. Harrison. Gut. 2008;57:1441.
4. Daniels. Hepatology. 2019;69:1075. 5. Sigrist. Theranostics. 2017;7:1303. 6. Jayaswal. AASLD 2018. Abstr. 1042.
6. Jayaswal. Liver Int. 2020;40:3071. 7. Idilman. Radiology. 2013;267:767. 8. Newsome. Lancet Gastroenterol Hepatol. 2020;5:362.
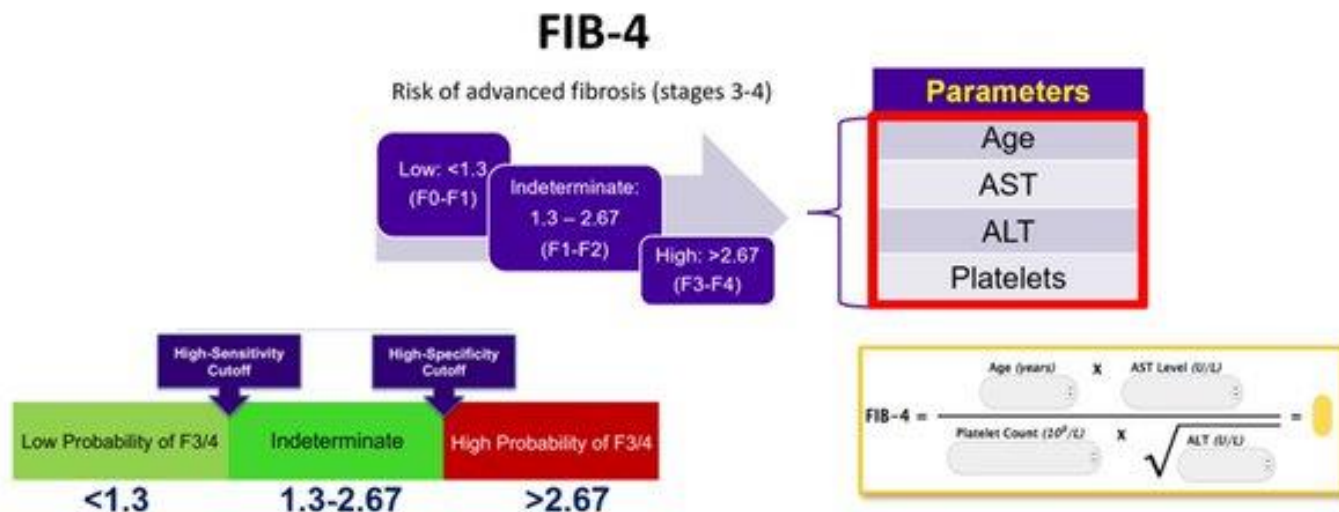
ALGORITME DE SEGUIMENT EN MAFLD
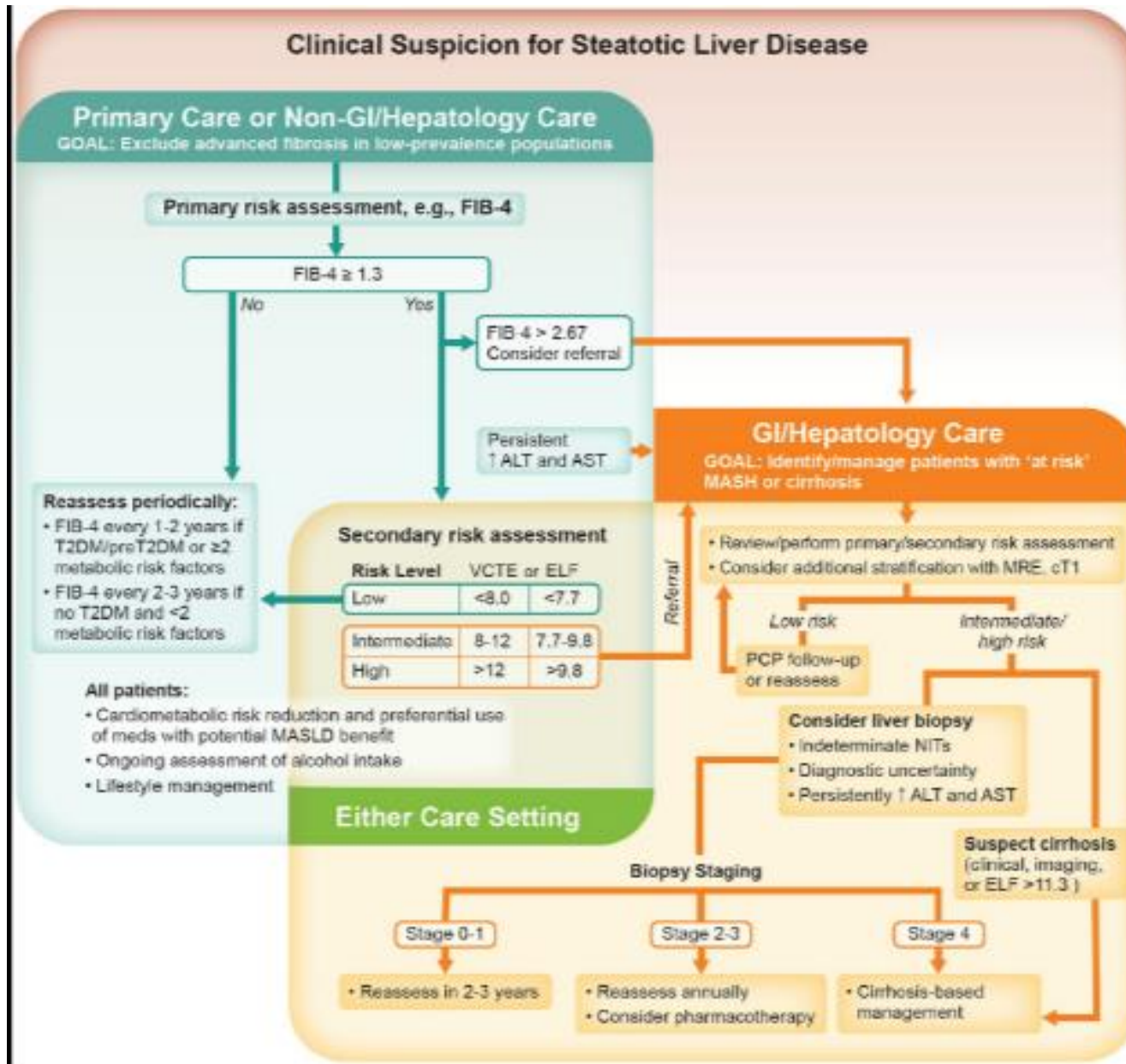
VALORACIÓ DE LA FIBROSIS PER FIB-4

Fibrosis-4 (FIB-4) Score
Simple Score for the Diagnosis of Advanced Fibrosis

- FIB-4 is the _most validated_ among the many tested to this end.
- Ability to predict changes over time in hepatic fibrosis.
- Allows risk stratification for future liver-related morbidity and mortality

FIB-4

Risk of advanced fibrosis (stages 3-4)

Low: <1.3
(F0-F1)

Indeterminate:
1.3 – 2.67
(F1-F2)

High: >2.67
(F3-F4)

Parameters

Age
AST
ALT
Platelets

High-Sensitivity Cutoff

High-Specificity Cutoff

Low Probability of F3/4	Indeterminate	High Probability of F3/4
<1.3	1.3-2.67	>2.67

$$FIB-4 = \frac{Age\ (years) \times AST\ Level\ (U/L)}{Platelet\ Count\ (10^9/L) \times \sqrt{ALT\ (U/L)}} =$$

Budd & Cusi, American Journal of Medicine, 2020

NAFLD Fibrosis Score

- Test per valorar la fibrosi hepática en NAFLD :
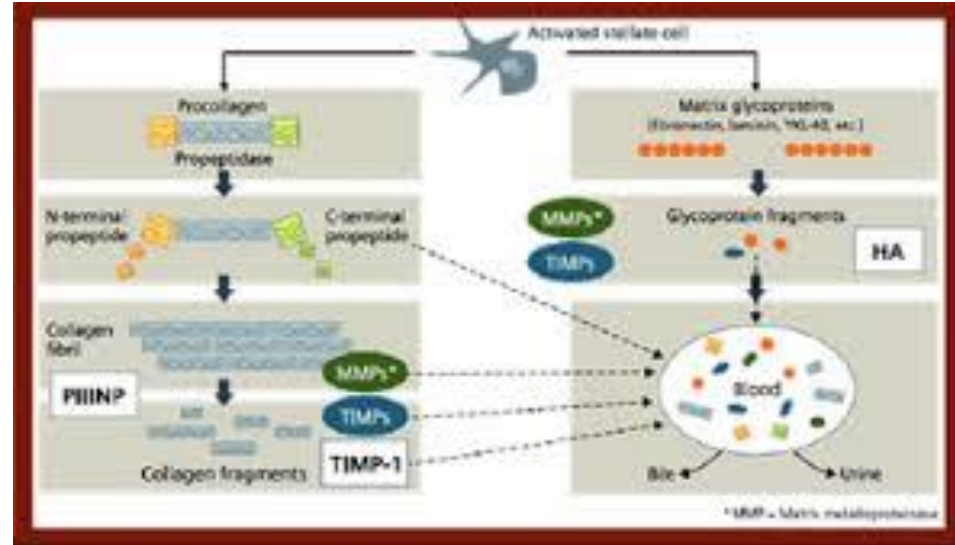
Edat, IMC, AST, ALT, Plaquetes, Albumina, Diabetes

NAFLD Fibrosis Score Range
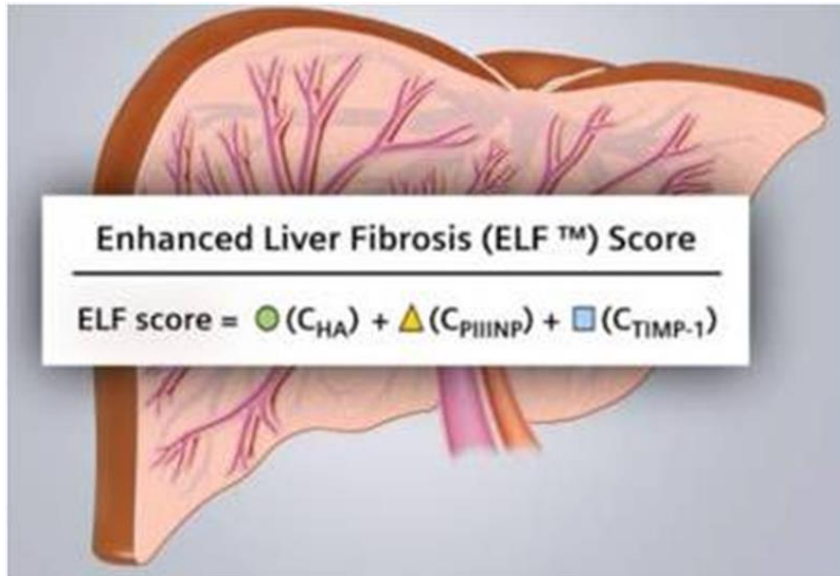
NAFLD Fibrosis Score	Interpretation
Less than -1.455	Low probability of fibrosis
From -1.455 to 0.676	Intermediate score
More than 0.676	High probability of fibrosis at baseline

Drlogy

Calculator

HELP!

www.drlogy.com

ELF Test

Enhanced Liver Fibrosis (ELF ™) Score

$$\text{ELF score} = \bullet\,(C_{HA}) + \triangle\,(C_{PIIINP}) + \square\,(C_{TIMP\text{-}1})$$

Table 2. ELF Score guidance

ELF Test Score	Interpretation	Action plan
>9.8	Likely severe fibrosis	Biopsy may not be required for liver fibrosis assessment
7.7-9.8	Uncertain may be moderate fibrosis	Biopsy may be recommended
<7.7	Likely no or mild fibrosis	Biopsy may not be required for fibrosis assessment

ALTRES BIOMARCADORS DE NASH - MAFLD

- *Marcadors d´apoptosi*: Fas, CK-18

- *Adipokines*: Adiponectina, TNF-α, IL-6

- *Marcadors metabòlics*: HOMA-IR, Growth factor receptor

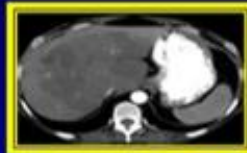- *Marcadors inflamatoris*: PCR

PROVES D´IMATGE NO INVASIVES

- *Ecografia abdominal*: hiperecogeneitat hepàtica

- *CT-Scaner*: disminució de l´atenuació hepàtica

- *RM* (no s´altera per obesitat, valorable per HCC)

- *Elastografia hepàtica* : permet valoració de Fibrosi (Kpa.) i Esteatosi hepàtica (dB/m.)

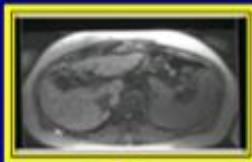Diagnostic Modalities for Fatty Liver

Schwenzer NF. *J Hepatol* 2009;51:433-45

AVALUACIÓ DE L´ESTEATOSI PER ELASTOGRAFIA - FIBROSCAN (**CAP**)

25 to 65 mm

F-1: < 7´1 kPa.
F-2: > 7´1 kPa.
F-3: > 9 kPa.
F-4: **> 13 kPa.**

S-1: CAP> 267 dB./m.
S-2: CAP> 279 dB./m
S-3: **CAP> 280 dB./m.**

3 cm^3

Stiffness

CAP

- fibrosis
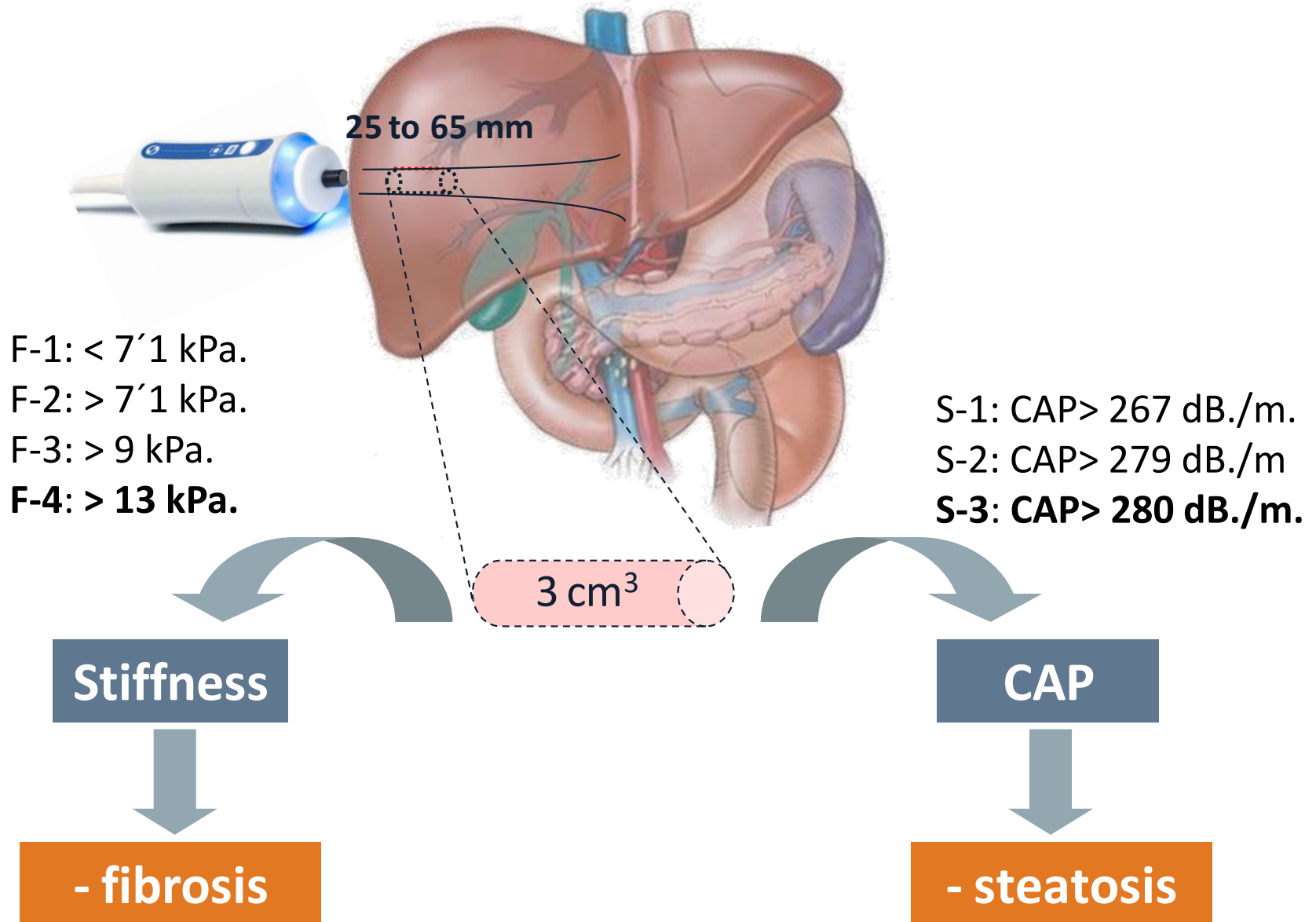
- steatosis

Interpretación de los resultados

- El valor de la elasticidad se correlaciona únicamente con el grado de fibrosis y no con el de actividad ni esteatosis

- La elasticidad o dureza hepática varía entre 2.5 y 75 Kpa

- Elasticidad   < 7 Kpa 93% F0 – F1

                   ≥ 7.6 Kpa 94% F2 o mayor (indicador de progresión)

2.5   7.0   9.5   12.5   75 kPa

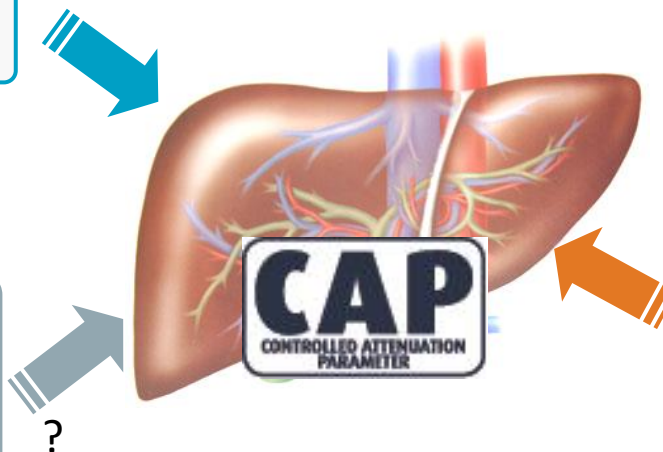**Ausencia o escasa fibrosis**   **Fibrosis significativa**   **Fibrosis severa**   **Cirrosis**

F3

METAVIR **F0-F1**   **F2**   (F3)   **F4**
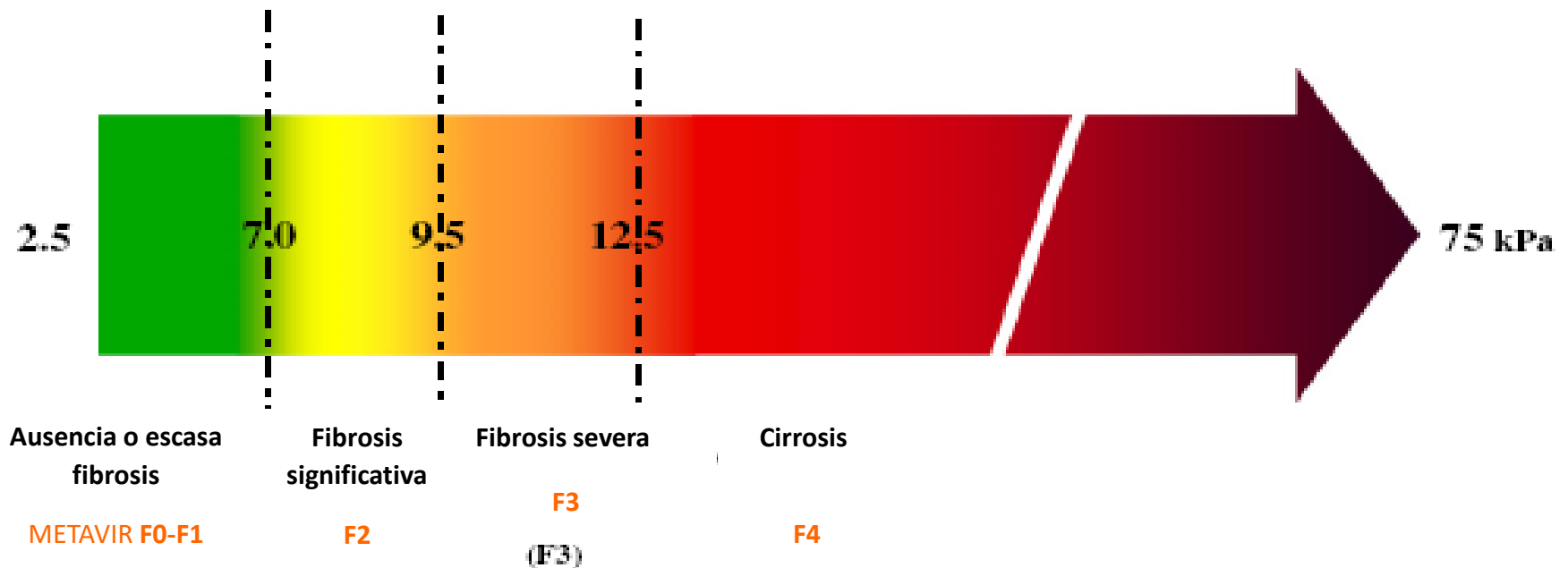
Factors influencing CAP

Influencing

- **Steatosis**
- **BMI**

Not ruled on yet

- **Stiffness**
- **Fibrosis**
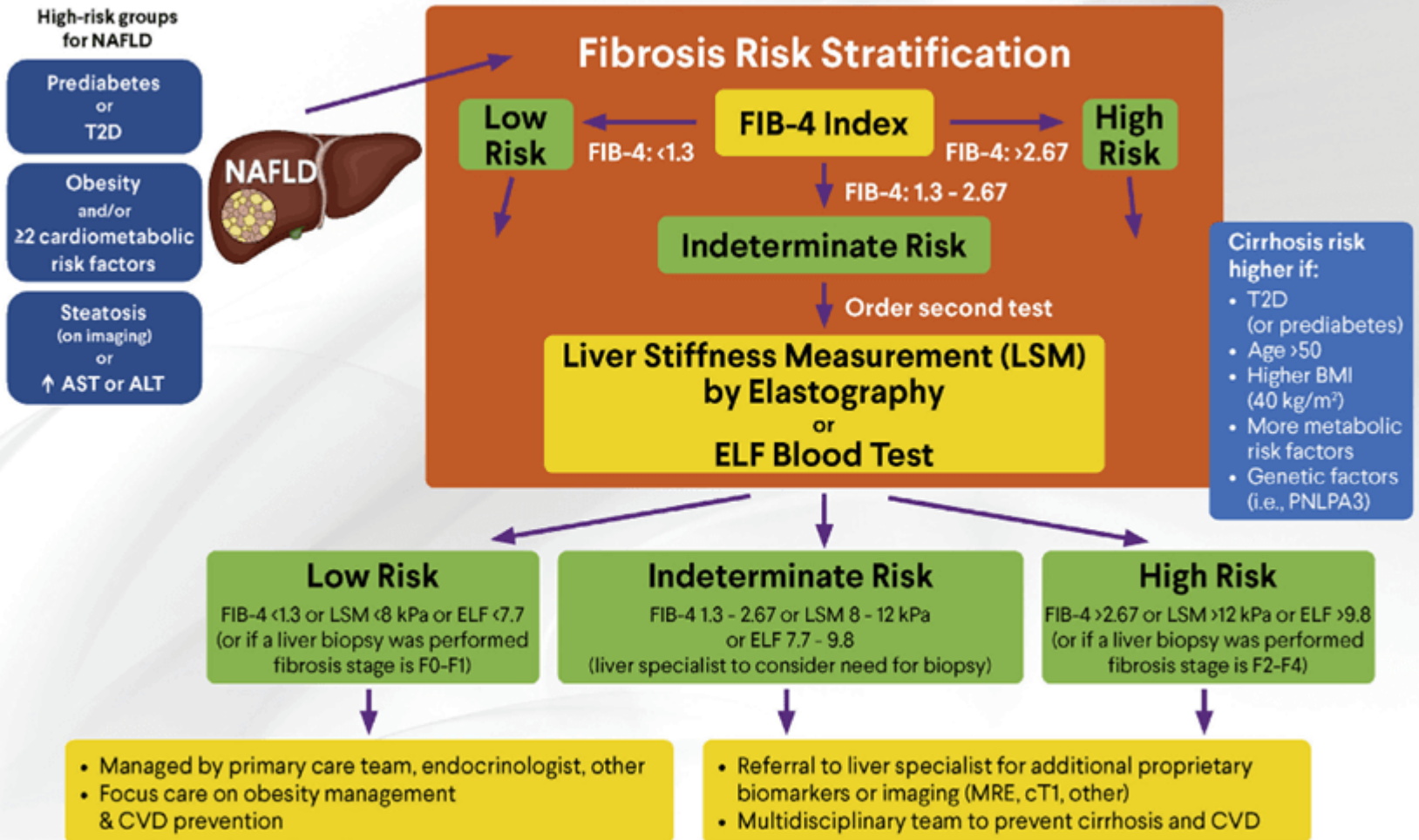- **Ballooning**
- **Aetiology**

?

Not influencing

- **Steato-hepatitis**
- **Inflammation**
- **Other histological parameters:**
  - ✓ Iron
  - ✓ Bilirubinostasis,
  - ✓ etc...
- **Transaminases**

CAP
CONTROLLED ATTENUATION PARAMETER

OBESITY → STEATOSIS → NASH → FIBROSIS → CIRRHOSIS → LIVER RELATED

50% → 30% → 50% → 20% → 30% → MORBIDITY & MORTALITY
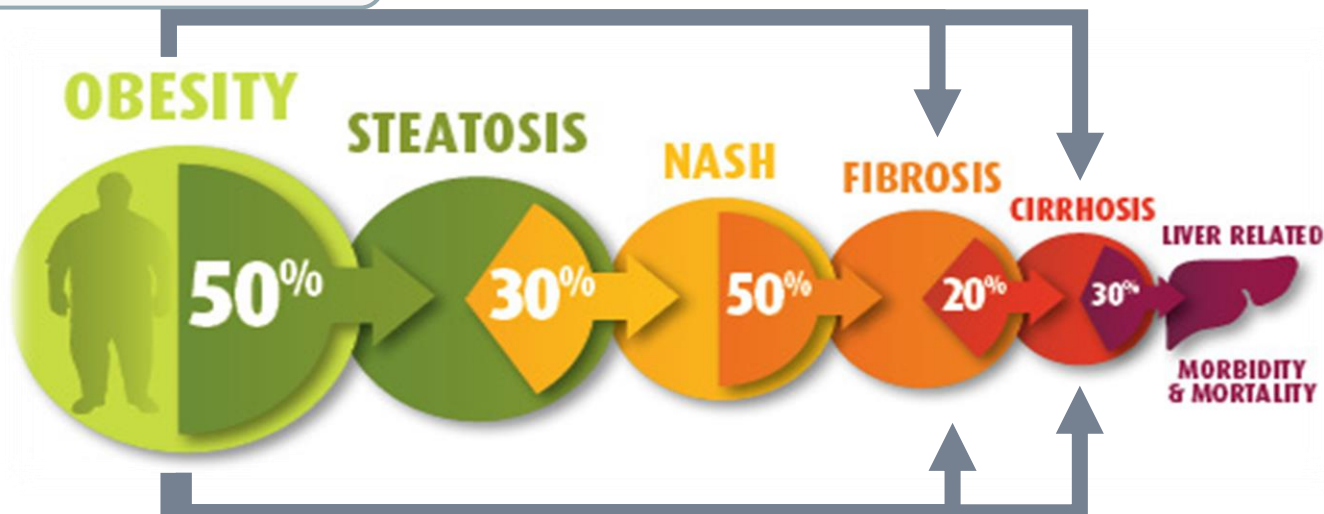
Cirrhosis Prevention in NAFLD

High-risk groups for NAFLD

- Prediabetes or T2D
- Obesity and/or ≥2 cardiometabolic risk factors
- Steatosis (on imaging) or ↑ AST or ALT

NAFLD

Fibrosis Risk Stratification

Low Risk ← FIB-4: <1.3 — **FIB-4 Index** — FIB-4: >2.67 → **High Risk**

FIB-4: 1.3 – 2.67 ↓

Indeterminate Risk

↓ Order second test

Liver Stiffness Measurement (LSM) by Elastography
or
ELF Blood Test

Cirrhosis risk higher if:
- T2D (or prediabetes)
- Age >50
- Higher BMI (40 kg/m²)
- More metabolic risk factors
- Genetic factors (i.e., PNLPA3)

Low Risk

FIB-4 <1.3 or LSM <8 kPa or ELF <7.7
(or if a liver biopsy was performed fibrosis stage is F0-F1)

↓

- Managed by primary care team, endocrinologist, other
- Focus care on obesity management & CVD prevention

Indeterminate Risk

FIB-4 1.3 - 2.67 or LSM 8 - 12 kPa or ELF 7.7 - 9.8
(liver specialist to consider need for biopsy)

↓

- Referral to liver specialist for additional proprietary biomarkers or imaging (MRE, cT1, other)
- Multidisciplinary team to prevent cirrhosis and CVD

High Risk

FIB-4 >2.67 or LSM >12 kPa or ELF >9.8
(or if a liver biopsy was performed fibrosis stage is F2-F4)

Abbreviations: ALT = Alanine aminotransferase, AST = Aspartate aminotransferase, cT1 = Liver multiscan, CVD = Cardiovascular disease, ELF = Enhanced liver fibrosis test™, FIB-4 = Fibrosis-4 index, kPa = Kilopascals, LSM = Liver stiffness measurement, MRE= Magnetic resonance elastography, T2D = Type 2 diabetes mellitus

Algorithm Figure 2

AACE.

ALGORITME EVOLUTIU

Liver health check in the endocrinology setting

- Viewpoint: Implementation of liver health check in patients with Type 2 Diabetes

- Analogous to screening/monitoring of other end organ damage

- Retino-, nephro- and neuropathy

- Cardiovascular Risk Management

- New nomenclature – MASLD/MASH - will help in case finding

Patient with T2D attends annual check

FIB-4<1.3

FIB-4 included in screening bloods if ≤75years

LSM<8kPa or ELF<9.8

FIB-4≥1.3

Transient elastography (>8kPa) OR ELF test (>9.8)

Specialist review

Diagnosis of cirrhosis

HCC screening

Portal hypertension management

Weight Loss Through Lifestyle Modification in NAFLD

| Weight Loss	Outcome Among Patients Achieving Weight Loss	Patients Sustaining Weight Loss at 1 Yr[1]
≥10%[1]	Fibrosis regression (45% of patients)[1]	<10%
≥7%[1]	NASH resolution (64%-90% of patients)*	18%
≥5%[1-3]	Ballooning/inflammation improvement (41%-100% of patients)*	30%
≥3%[1-4]	Steatosis improvement (35%-100% of patients)*	Not reported

*Depending on degree of weight loss.

1. Vilar-Gomez. Gastroenterology. 2015;149:367. 2. Promrat. Hepatology. 2010;51:121.
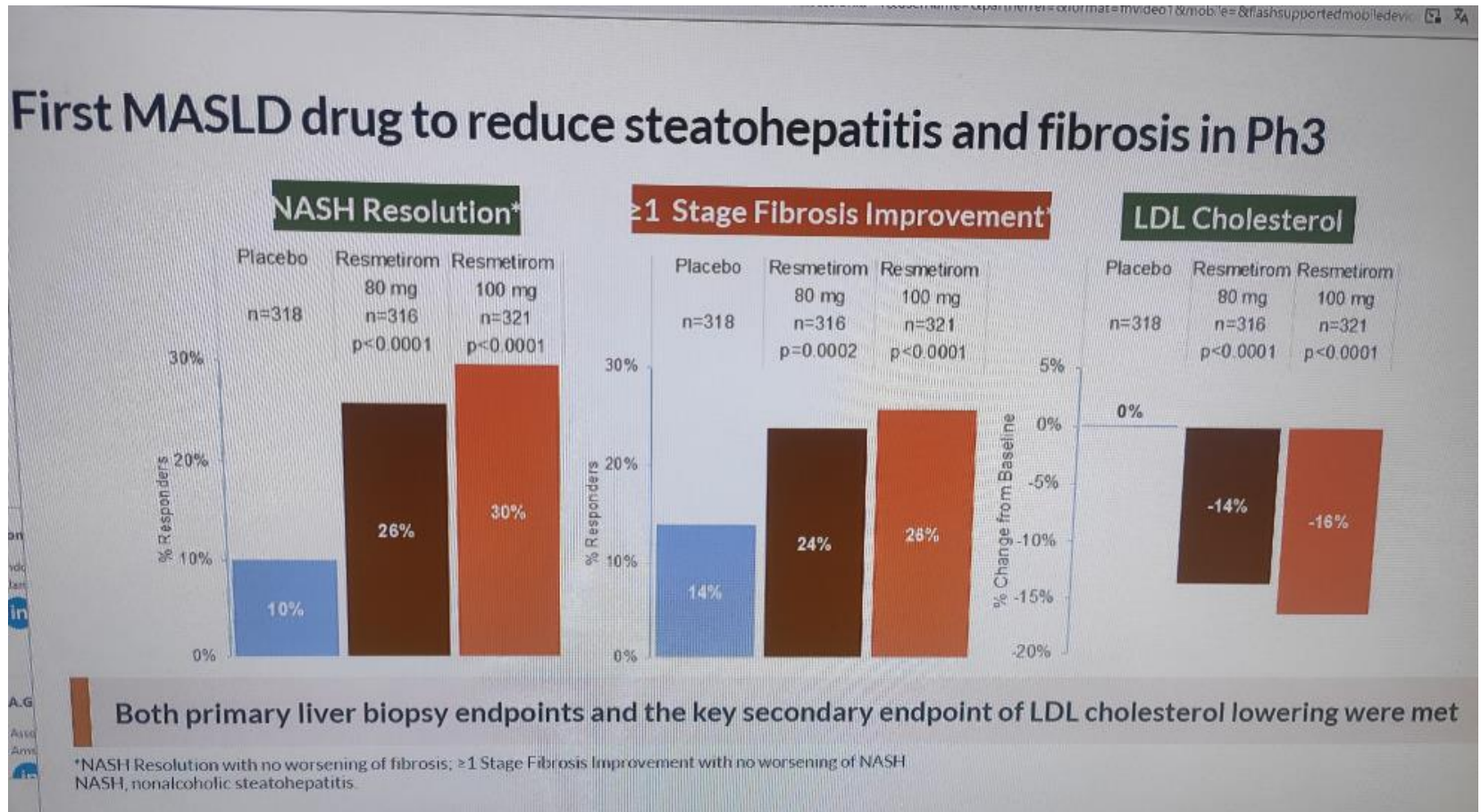3. Harrison. Hepatology. 2009;49:80. 4. Wong. J Hepatol. 2013;59:536.

Potential Therapeutic Targets in NASH
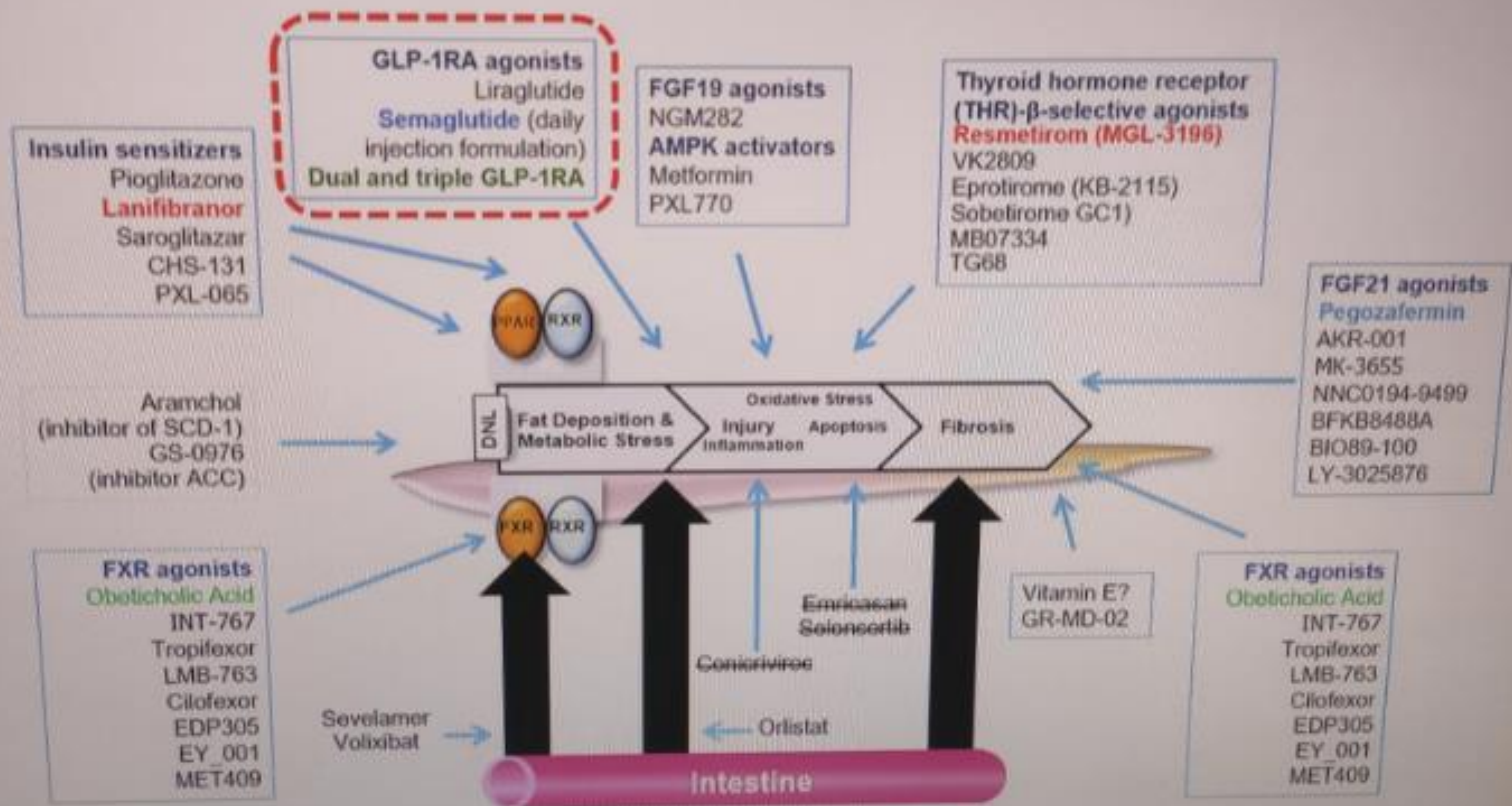
RESMETIROM (Rezdiffa ®) x FDA

First MASLD drug to reduce steatohepatitis and fibrosis in Ph3

Millora inflamació dels hepatòcits
Millora de la Fibrosi hepática
Disminueix el Colesetrol – LDL
Regula el metabolisme lipídic

A Phase 3, Randomized, Controlled Trial of Resmetirom in NASH with Liver Fibrosis

Harrison SA et al.   DOI: 10.1056/NEJMoa2309000

CLINICAL PROBLEM

Nonalcoholic steatohepatitis (NASH) is a progressive liver disease characterized by ≥5% hepatic steatosis with hepatocellular damage and inflammation. There are currently no approved pharmacologic treatments for NASH. Resmetirom is an oral, liver-directed, thyroid hormone receptor beta–selective agonist in development for the treatment of NASH.

Fibrosis Stages

F0 F1 F2 F3 F4

Placebo (N=321)

Resmetirom 80 mg (N=322)

Resmetirom 100 mg (N=323)

Fibrosis stages range from F0 (no fibrosis) to F4 (cirrhosis)

CLINICAL TRIAL

Design: An ongoing, phase 3, multinational, double-blind, randomized, placebo-controlled trial assessed the efficacy and safety of resmetirom in adults with biopsy-confirmed NASH and liver fibrosis.

Intervention: 966 patients with NASH and fibrosis of stage F1B, F2, or F3 were assigned in a 1:1:1 ratio to receive once-daily resmetirom (80 mg or 100 mg) or placebo. The two primary end points at week 52 were NASH resolution (including a reduction in the nonalcoholic fatty liver disease [NAFLD] activity score by ≥2 points; scores range from 0 to 8, with higher scores indicating more severe disease) with no worsening of fibrosis, and an improvement (reduction) in fibrosis by ≥1 stage with no worsening of the NAFLD activity score.

Primary End Points

Placebo (N=318) Resmetirom, 80 mg (N=316) Resmetirom, 100 mg (N=321)

NASH Resolution with No Worsening of Fibrosis: Placebo 9.7, Resmetirom 80 mg 25.9 (P<0.001), Resmetirom 100 mg 29.9 (P<0.001)

Fibrosis Improvement by ≥1 Stage with No Worsening of NAFLD Activity Score: Placebo 14.2, Resmetirom 80 mg 24.2 (P<0.001), Resmetirom 100 mg 25.9 (P<0.001)

RESULTS

Efficacy: Among evaluable patients, both doses of resmetirom were superior to placebo with respect to the two primary end points.

Safety: More than 90% of the patients in each group had adverse events, most of which were mild or moderate in severity. Diarrhea and nausea occurred more often with resmetirom than with placebo. The incidence of serious adverse events was similar among the groups.

Safety

Placebo (N=321) Resmetirom, 80 mg (N=322) Resmetirom, 100 mg (N=323)

Diarrhea: Placebo 15.6, Resmetirom 80 mg 27.0, Resmetirom 100 mg 33.4

Nausea: Placebo 12.5, Resmetirom 80 mg 22.0, Resmetirom 100 mg 18.9

Serious Adverse Event: Placebo 11.5, Resmetirom 80 mg 10.9, Resmetirom 100 mg 12.7

LIMITATIONS AND REMAINING QUESTIONS

- The trial lacked clinical-outcomes data to correlate with the histologic data. The trial is planned to continue to 54 months to evaluate liver-related outcomes, including progression to cirrhosis.
- Almost 90% of the participants were White, which limits the generalizability of the findings to other racial or ethnic groups.

Links: **Full Article | NEJM Quick Take | Editorial**
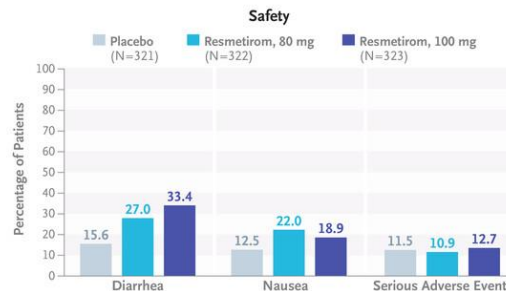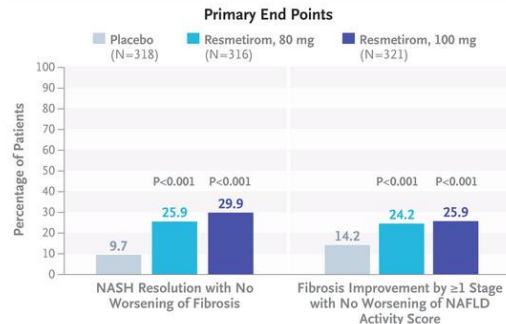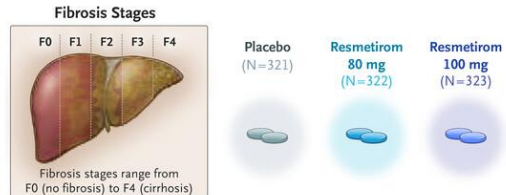
CONCLUSIONS

In patients with NASH and liver fibrosis, once-daily treatment with resmetirom was superior to placebo with respect to NASH resolution and fibrosis improvement by ≥1 stage at 52 weeks of follow-up.

GRACIES